

RUNX1a enhances hematopoietic lineage commitment from human embryonic stem cells and inducible pluripotent stem cells.

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Public Summary:

Advancements in research of human pluripotent stem cells, including both embryonic stem cells and induced pluripotent stem cells, have potential to revolutionize therapeutic blood cell transplantation. It has been demonstrated that transcription factors may play key roles in regulating maintenance, expansion, and differentiation of pluripotent stem cells. In addition to its regulatory functions in blood cell formation and blood-related disorders, the transcription factor RUNX1 is also required for the formation of adult blood stem cells. In the current study, we demonstrated that expression of endogenous RUNX1a, an isoform of RUNX1, parallels with lineage commitment and hematopoietic formation from human embryonic stem cells and inducible pluripotent stem cells. In a defined blood cell differentiation system, increased expression of RUNX1a facilitates generation of blood precursor cells. RUNX1a expressing precursor cells show enhanced expansion and are capable of differentiating into multiple types of blood cells. Expression of RUNX1a in embryoid bodies derived from pluripotent stem cells promotes adult red blood cell formation. Moreover, when RUNX1a expressing blood precursor cells were transplanted into immunodeficient mice, multiple types of human blood cells can be detected in mice for at least nine weeks. Together, our results suggest that RUNX1a facilitates the process of producing blood cells from pluripotent stem cells.

Scientific Abstract:

Advancements in human pluripotent stem cells (hPSCs) research have potential to revolutionize therapeutic transplantation. It has been demonstrated that transcription factors may play key roles in regulating maintenance, expansion, and differentiation of hPSCs. In addition to its regulatory functions in hematopoiesis and blood-related disorders, the transcription factor RUNX1 is also required for the formation of definitive blood stem cells. In the current study, we demonstrated that expression of endogenous RUNX1a, an isoform of RUNX1, parallels with lineage commitment and hematopoietic emergence from hPSCs, including both human embryonic stem cells and inducible pluripotent stem cells. In a defined hematopoietic differentiation system, ectopic expression of RUNX1a facilitates emergence of hematopoietic progenitor cells (HPCs) and positively regulates expression of mesoderm and hematopoietic differentiation related factors, including Brachyury, KDR, SCL, GATA2, and PU.1. HPCs derived from RUNX1a-hPSCs show enhanced expansion ability and the ex vivo expanded cells are capable of differentiating into multiple lineages. Expression of RUNX1a in embryoid bodies (EBs) promotes definitive hematopoiesis that generates erythrocytes with beta-globin production. Moreover, HPCs generated from RUNX1a-EBs possess at least 9 weeks repopulation ability and show multi-lineage hematopoietic reconstitution in vivo. Together, our results suggest that RUNX1a facilitates the process of producing therapeutic HPCs from hPSCs.

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